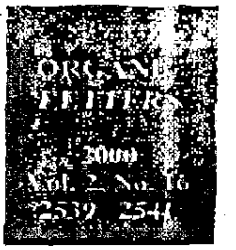

A Novel and Effective Procedure for the Preparation of Glucuronides

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ABSTRACT

Donor or Acceptor

6-Phenylthio-6-deoxy-D-glucopyranosides were easily prepared from 6-hydroxy-D-glucopyranosides and employed as effective glycosyl donors or acceptors. And the resulting coupling products were then readily converted into the corresponding D-glucuronide-containing compounds.

Glucuronide is an integral component in proteoglycans which play essential roles in many cellular processes, including cell growth and cell−cell interactions.[1] Glucuronide exists also as an important structural unit in a number of bacterial capsular polysaccharides and plant glycosides which show promising biological activities.[2,3] Furthermore, glucuronide is frequently the final form of a drug or xenobiotic eliminated from the body, often performing a detoxification role.[4] As a consequence of these biological rationales, development of synthetic schemes for glucuronides has been targeted by many investigators.[4,5] Although most of the methods employed for glucuronide synthesis have their parallel in glucopyranoside synthesis, glucuronide donors or acceptors have been found to be more sluggish than the corresponding glucopyranoside counterparts. Schmidt and co-workers have in fact classified glycuronide donors as the type of glycosyl donor with the lowest reactivity.[5] The distinctive chemistry of glucuronides has been attributed to the electron-withdrawing 5-carboxyl group, which remarkably decreases the nucleophilicity of the hydroxy groups on glucuronide acceptors, or exerts a destabilizing effect on the incipient C-1 cation leading to the low reactivity of glucuronide donors. Consequently, coupling with glucuronide donors or acceptors usually gives low yields of the products.[4] Oscarson et al. therefore have recently developed ethyl thio-glucuronide donors with activating protective groups (benzyl or silyl) at O-3 and O-4 and a neighboring participating group at O-2.[7] Alternatively, glucuronides, glucuronide-containing oligosaccharides in particular, are often synthesized by introduction of the carboxyl group at a later oxidation step after coupling with a glucopyranoside moiety.[5] However, this approach requires extensive protective group manipulations for selectively generating a free 6-OH at a later stage.

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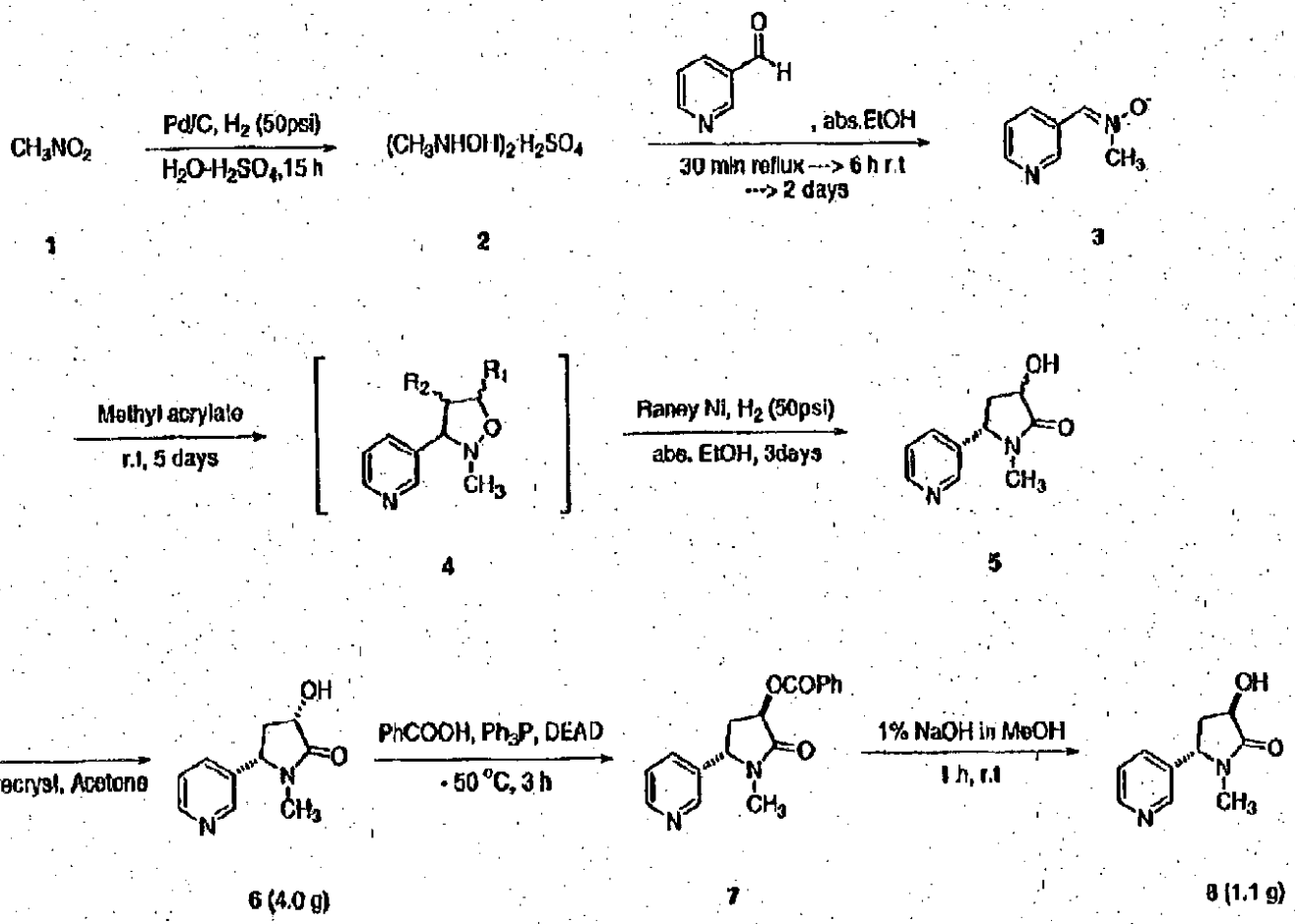
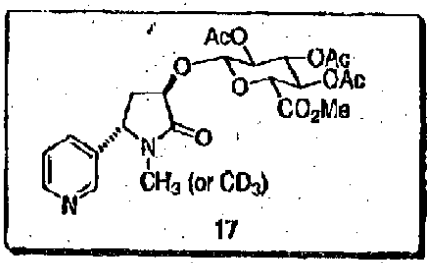
trans-3'-Hydroxycotinine



1 2 3 4 5 6 (4.0 g) 7 8 (1.1 g)

trans-3'-Hydroxycotinine-d_3



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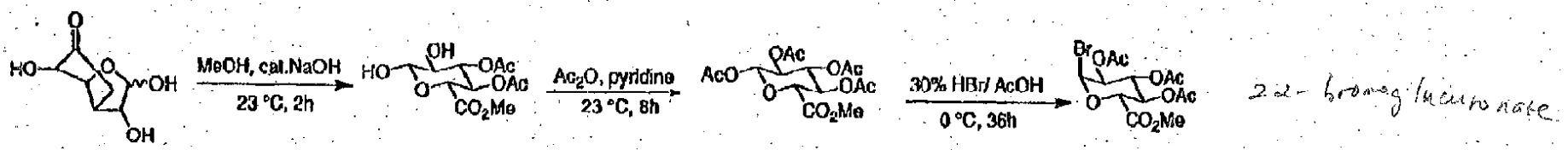
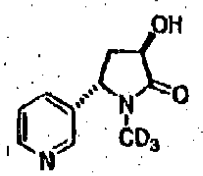


18 D-glucurono-3,6-lactone

19

20 (40% overall)

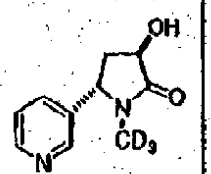
21 (85%) 2,4-bromoglucuronate



5

"various conditions"

17



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"various conditions"

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